This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

BA

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61B 5/05, 5/0205	A1	(11) International Publication Number: WO 98/53737
		(43) International Publication Date: 3 December 1998 (03.12.98)

(21) International Application Number: PCT/IL97/00174

(22) International Filing Date: 30 May 1997 (30.05.97)

(71) Applicant *(for all designated States except US)*: N.I. MEDICAL LTD. [IL/IL]; Maskit Street 22, 46733 Herzliya Pituach (IL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: TSOGLIN, Alexander [IL/IL]; Habarzel Street 31, Ramat Hachayal, 69710 Tel Aviv (IL). FRINERMAN, Efim [IL/IL]; Livorno Street 9/28, 59644 Bat Yam (IL).

(74) Agent: REINHOLD COHN AND PARTNERS; P.O. Box 4060, 61040 Tel Aviv (IL).

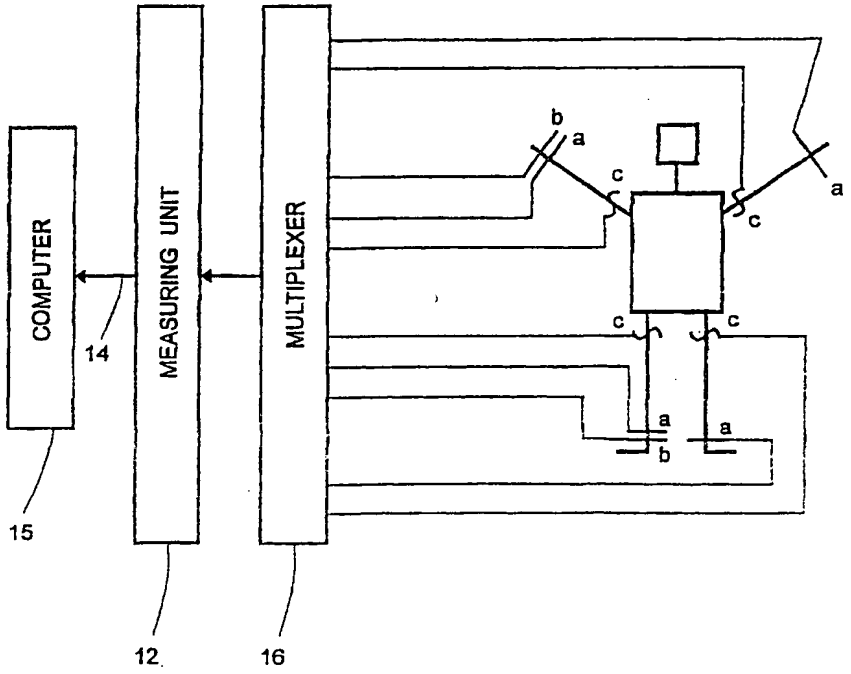
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: METHOD AND SYSTEM FOR NON-INVASIVE DETERMINATION OF THE MAIN CARDIORESPIRATORY PARAMETERS OF THE HUMAN BODY

(57) Abstract

A method and a system for non-invasively determining at least one main cardiorespiratory parameter of an individual, such as the Stroke Volume, at least one parameter characterizing balance of the extracellular fluid in the body (such as the Index Balance), and for diagnostics of blood circulatory problems and/or failures of cardiac functions. The method for determining the main cardiorespiratory parameter comprises the steps of attaching at least two electrodes to the individual's body in a manner enabling to obtain electrical bioimpedance measurements of the whole individual's body, passing an alternating current with a stable and constant amplitude through the electrodes, measuring the integral bioimpedance as the result of the current flow; simultaneously separating an active component from the integral bioimpedance; calculating the cardiorespiratory parameter of the individual from the obtained active component, using an empiric formula applicable to integral bioimpedance measurements. The calculation is based on obtaining a number of values of the parameter for a number of cardia cycles during a respiratory cycle, and computing an average of the cardiorespiratory parameter during a single respiratory cycle.



Method and System for Non-Invasive Determination of the Main Cardiorespiratory Parameters of the Human Body

FIELD OF THE INVENTION

The present invention relates to non-invasive cardiac and respiratory monitors, more particularly, to such systems for determining cardiac and respiratory performance using electrical bioimpedance measurements.

BACKGROUND OF THE INVENTION

U.S. Patent No. 5,469,859 discloses a non-invasive method and device for determination of the main cardiovascular parameters of a patient's body. In this method two or four electrodes are applied to the patient's body in a manner enabling the measurement of total body (integral) bioimpedance. High stability amplitude alternating current is passed through the body by the electrodes to allow the obtaining of an integral impedance curve and derivation therefrom of an active (resistive) component. The cardiorespiratory parameters of the body are calculated from the active component, using an empiric formulae, with the calculation being based on the average data obtained during a respiration cycle.

OBJECT OF THE INVENTION

It is an object of the present invention to provide an improved, more accurate non-invasive electric bioimpedance measurement (EBM) method and system for the determination of the main cardiorespiratory parameters of the human body and for diagnosis of diseases or malfunctions of the cardiorespiratory and of the blood circulation system.

SUMMARY OF THE INVENTION

The invention provides by a first of its aspects, a non-invasive method for determining the main cardiorespiratory parameters of an individual. In accordance with this aspect, electrodes are applied to at least two of the individual's arms and legs, a high stability amplitude alternating current is injected through the electrode into the body, and an impedance curve is thus obtained. An active (i.e. resistive) component is then separated from the impedance and by employing an empiric formula applicable to integral bioimpedance measurements, cardiorespiratory parameters of the individual are calculated from said active component. By differentiating measurements of these parameters between electrode attachments on different extremities (arms or legs) blood circulation problems and other diseases may be diagnosed.

More specifically, in accordance with a first aspect of the invention, there is provided a method for non-invasively determining at least one main cardiorespiratory parameter of an individual, comprising the steps of:

attaching at least two electrodes to the individual's body in a manner ensuring a low impedance contact between the electrodes and the individual's skin, and positioning the electrodes so that current which passes between the at least two electrodes flows between at least one arm or at least one leg to at least another arm or at least another leg of the individual;

passing an alternating current with a stable and constant amplitude through said at least two electrodes and at the same time, measuring the potential change as the result of the current flow, whereby an electrical bioimpedance measurement of the individual's body from the measured potential between the said at least two electrodes is obtained;

simultaneously separating an active component from said bioimpedance;

calculating the at least one cardiorespiratory parameter of said individual from the active component of said bioimpedance, using an empiric formula applicable to integral bioimpedance measurements, in such

a manner so as to obtain a number of values of said at least one parameter for a number of cardiac cycles during a respiratory cycle, and calculating an average of said at least one parameter during a single respiratory cycle; and

displaying the average cardiorespiratory parameters thus obtained.

Owing the particular mode of averaged calculation of the cardiorespiratory parameter during a respiratory cycle as defined in the above method, it improves accuracy of measurements provided according to the method disclosed in the prior art. This mode will be further explained and illustrated below with reference to one of the attached drawings (Fig. 1)

It has also been found by the inventors, that the step of separating an active component from the measured bioimpedance curve enables to calculate, with high accuracy, the main cardiorespiratory parameters of an individual even if this curve is not the integral bioimpedance curve of the total body (i.e. not the measurement across the whole individual's body).

Moreover, owing to the high accuracy of the new method it may be successfully performed not only for determining the main cardiorespiratory parameters, but also for specific diagnostic purposes using "arm–leg", "arm–arm" and "leg–leg" electrode placements and comparing the respective measurements, as will be described later on.

The basic hemodynamic parameter Stroke Volume (SV) may be calculated according to the following semi–empiric formula applicable to integral bioimpedance measurements:

$$SV = \frac{Hct_{corr.}}{K(shape*sex*age)} * \delta r \frac{H^2_{corr.}}{R} * \frac{\alpha + \beta}{\beta} * Kel * Kw * IB \qquad (1)$$

where:

$Hct_{corr.}$ a correcting factor depending from Hematocrit, being $145 + 0.35(Hct - 40)$;

Hct Hematocrit, obtained from the blood analysis of the individual;

*K(shape*sex*age)* a coefficient of the individual's body, being:

men younger than 20 years old = 527.3 –(3.1 * (Actual Age –20));

women younger than 18 years old = 587.6 –(2.9 * (Actual Age –18));

men from 20 to 40 years old = 527.3;

women from 18 to 50 years old = 587.6;

men older than 40 years old = 527.3 + (3.1 * (Actual Age –40));

women older than 50 years old = 587.6 + (2.9 * (Actual Age –50));

$\delta r/R$ the ratio characterizing the measured active bio–impedance component's change, δr, with respect to the individual's body resistance R

δr the amplitude value of the change of the individual's body basic resistance R on the anacrotic (systolic) portion of a cardiocycle.

R basic resistance of the individual's body during one cardiocycle.

$H_{corr.}$ the corrected height of the patient, given by:

$$H_{corr} = (H_{real} + 2) \quad \text{if} \quad \frac{\text{legs length}}{\text{body length}} = 0.66 \pm 0.04$$

or

$$H_{corr} = (H_{real} - 2) \quad \text{if} \quad \frac{\text{legs length}}{\text{body length}} = 0.54 \pm 0.04 \qquad (2)$$

or

$$H_{corr} = (H_{real}) \quad \text{if} \quad 0.62 \geq \frac{\text{legs length}}{\text{body length}} \geq 0.58$$

$\alpha + \beta$ duration of a cardiac cycle, being a sum of its anacrotic and catacrotic parts;

β duration of the catacrotic part of a cardiac cycle;

Kel coefficient of electrolytic ions in the individual's blood, calculated based on the blood analysis and being given by:

a) for an individual exposed to a hemodialysis

$$Kel = \frac{(Na^+ + K^+ + Mg^+ + Ca^+)\ (\text{mmol/l})}{142 + 13\ (\text{mmol/l})} \qquad (3)$$

b) for other individuals

$$Kel = \frac{(Na^+)\ (\text{mmol/l})}{142\ (\text{mmol/l})} \qquad (4)$$

K_w the weight coefficient, being $\frac{\text{Actual weight}}{\text{Ideal weight}^*}$

* (according to the International Tables of ideal weights)

IB Index Balance, reflecting ratio between the measured volume of extracellular fluids and the individual's proper volume of extracellular fluids. This is calculated on the basis of a formula for the *"ideal content of body water"*, adapted from Kushner, R.T. *et al.*, (*Amer. J. Clin. Nutr.*, 44:417–424, 1986):

$$IB = \frac{\text{R individual's proper}}{\text{R measured}} \qquad (5)$$

where: R measured – the individual's active (resistive) component of the bioimpedance measured either by tetrapolar mode, or by bipolar mode with correction to the individual's skin resistance.

In accordance with the invention, R individual's proper is calculated according to the two following formulae:

$$\frac{0.42H^2}{0.47W - 8.30} \quad \text{for men}$$

(6)

$$\frac{0.42\ H^2}{0.37\ W - 4.96} \quad \text{for women}$$

where H – the individual's height

W – the individual's weight

The above described novel equation (1) demonstrates that individual differences in bioimpedance of a specific human body can be considered by correcting the formula according to the particular features of the individual's body.

The electrodes may, in principle, be attached to any portion of the individual's extremities, and preferably to distal parts thereof.

The method in accordance with the invention can be carried out either in a bipolar or a tetrapolar mode. In accordance with a bipolar mode of carrying out the invention, at least two electrodes are utilized, wherein any electrode attached to an arm or a leg is used both for current injection and voltage measurement. In accordance with a tetrapolar mode of carrying out the invention, at least four electrodes are utilized; different electrodes are used for current injection than those which are used for voltage measurement. Thus, in accordance with the latter mode of the invention, the arm or leg under examination is typically fitted with two electrodes, the current injection being between a first pair of electrodes located each on a different arm or leg, and the voltage is measured by a second pair of electrodes, located on same, respective, arm or leg.

When performing the bipolar mode of the invention, two electrodes are usually utilized. Where two electrodes are being used they

are typically attached, one to an arm and the other to a contralateral leg. However, it is possible to determine the main cardiorespiratory parameters by attaching the two electrodes to the two arms of the individual, to the two legs, or to one arm and one semi-lateral leg. Although the attachment of one electrode to an arm and the other to a contralateral leg is preferred, the other mode of attachments may at times be used where an arm or a leg are diseased in a manner which avoids attachment and/or obtaining accurate or reliable readings.

In accordance with another embodiment of the bipolar mode of the invention, two electrodes connected to one another are attached to each of the individual's arms, and another two electrodes, again connected to one another, are attached to each of the individual's legs. In accordance with this embodiment, the current in injected in parallel between the two arms and the two legs and the voltage is simultaneously measured also between the two arms and the two legs.

All the electrode's placements described above for the bipolar mode may be applied also for the tetrapolar mode (the difference being in that rather than a single electrode at each site, there will be two such electrodes in accordance with the tetrapolar mode).

It is important, that the skin resistance of an individual may differ from time to time and the different skin resistances may have an effect on the measured results. In order to measure skin resistance, in accordance with a second aspect of the invention, an auxiliary pair of current injecting electrodes is used in addition to the standard pair of current injecting electrodes applied in accordance with the bipolar mode described above, and constituting also the voltage measuring electrodes. The auxiliary current injecting electrodes are attached so that each one of the pair of such electrodes is placed at a certain distance, e.g. about 4 cms., away from the respective standard electrodes. For example, where the standard electrodes are placed one attached to an arm and the other attached to a contralateral leg, the auxiliary current injecting electrodes will be placed on the same arms and legs, a certain distance from the standard electrode pair.

Typically, the auxiliary electrodes will be placed to be more distal than the standard electrodes.

In accordance with this second aspect, current will first be passed through the standard electrodes and voltage will be measured by the same standard electrodes. Current will then be passed through the auxiliary electrodes and voltage will be measured again between the standard electrodes, the difference in measured voltage being accountable for the skin resistance.

In other words, the standard measurement is made by utilizing the bipolar mode, but for the auxiliary measurement the tetrapolar mode is used, in which the electrodes utilizing the bipolar mode serve then for voltage measurement only. Thus in a skin resistance measurement, there will typically be a combination of the bipolar and tetrapolar modes.

The skin resistance in a combined bipolar/tetrapolar measurement mode as described above, is thus determined by the following formula:

$$R_s = R_1 - R_2 \qquad (7)$$

wherein R_s – is the skin resistance, i.e. resistance between the current injection electrode and the skin in the bipolar mode,

R_1 – is the individual's resistance measured between two electrodes according to the bipolar mode, and

R_2 – is the resistance measured in the same individual when applying the tetrapolar mode.

When using the bipolar mode, the measured active component of the individual's bioimpedance, which forms a basis for the calculation of main cardiorespiratory parameters, constitutes R_1. Since the value of skin resistance R_s may vary during the measurements, the value of the measured

resistive component should be adjusted, so as to reduce the error of measurement.

Moreover, the skin resistance may have also a separate diagnostic significance.

The general approach in the art, for example that of Lukaski, *et al.*, (*The American Journal of Clinical Nutrition*, 41:810-817, 1985) states that various configurations of electrode's placement (i.e., arm-leg, leg-leg, arm-arm) do not substantially affect results of whole body EBM measurements, more particularly, measurements of the resistive component R of the bioimpedance. However, when carrying out the method of the invention, it was found that results obtained at different electrodes' configurations may be somewhat different from one another, and therefore by comparison of such different results, it is possible to obtain information having a diagnostic significance.

For example, where the parameters are obtained by measuring between an individual's two arms (an *"arm-arm"* placement), the readings obtained are influenced primarily by the pulmonary circulatory system and functions of the individual's right ventricle. When the parameters are obtained by an *"arm-leg"* placement, the results will characterize a systemic circulation (represented mainly by the aorta) and thus will reflect functions of the individual's left ventricle.

As will be appreciated, in a healthy individual, the results obtained with the mentioned two electrode's placements (arm-arm and arm-leg) will be substantially the same. However, at different pathological situations, particularly where the individual has certain cardiorespiratory diseases, there will be a difference between the results obtained at the two electrode placements and such differences, possibly with the aid of additional measurement as will be detailed below, may be used to diagnose the cite and type of the disturbance.

The above-mentioned differences may be correctly detected and interpreted where the individual's extremities to which the electrodes are attached, do not have blood circulation problems. Thus, in order to allow

proper interpretation of such results, errors which may be introduced by disturbances in the peripheral blood circulation, should be excluded. The following is an example of the sequences of steps to exclude such errors and to allow a preliminary functional diagnosis of such disturbances. However, it should be appreciated, that the same sequences of steps also represent independent methods of functional diagnosis of blood circulation.

Step 1: Examination of the peripheral blood circulation

For examination of the peripheral circulation, parameter P, represented by the following equation (8) (see below) and forming part of the equation (1) can be chosen:

$$P = \delta r \frac{H^2 corr}{R} * \frac{\alpha + \beta}{\beta} \qquad (8)$$

Alternatively, or in addition, portions of the equation (8) may be used as parameters P_1, P_2 or P_3 represented by the following formulae (9–11):

$$P_1 = \frac{\delta r}{R} \qquad (9)$$

$$P_2 = \frac{H^2 corr}{R} \qquad (10)$$

$$P_3 = \frac{\alpha + \beta}{\beta} \qquad (11)$$

The peripheral circulation, i.e. the circulation in the arms and legs is checked using the basic *"leg–leg"*, *"arm–arm"*,and *"arm–leg"*connectivity configurations together with an addition connectivity configurations, which include measurement between pairs of electrodes, one situated at a distal part of an arm or leg and the other on the shoulder or hip.

The readings of P and P_1–P_3 which are obtained using the *"leg–leg"* configuration are characteristic primarily of the individual's peripheral blood circulation (i.e., without the aorta and the pulmonary arteries). Where the above mentioned parameters obtained in a *"leg–leg"* electrode placement are substantially different from the ones obtained by the *"arm–arm"* and *"arm–leg"* placements, this may be indicative of peripheral circulatory problems, mainly such associated with an individual's legs.

In order to reveal a circulation related pathology in the leg, a pair of additional electrodes may be attached to the individual's hips, to provide EBM measurements between the distal parts of the leg and the hip for each leg. Values of P and P_1 to P_3 which are obtained for both legs, may then be compared to one another and with the value of the proper P and proper P_1 to P_2, for the individual (i.e. values for these parameters which are obtained with R proper – see equation (6).

A pathologic arm may be diagnosed in an analogous manner applying additional electrodes to the shoulders of the individual, obtaining readings of P and P_1–P_3, and processing thereof, in a similar manner as in the leg.

In order to measure the Stroke Volume parameter (SV), either one of the above-noted *"arm–arm"* and *"leg–arm"* connectivity configurations may be used. However, in order to allow derivation of left ventricle Stroke Volume and right ventricle Stroke Volume, a more complicated so called *"arm–arm–leg"* connectivity configuration is required to obtain a multi channel bioimpedance measurement, i.e., *"arm–arm"* and *"arm–leg"* measurements are typically performed by automatic multiplexing. In order to obtain such multi channel measurement, it is thus necessary that the two arms of the individual will be healthy and that the individual will have at least one healthy leg (it should be noted that conditions where individuals have arms with circulatory problems, are very rare).

In order to obtain measurements characterizing left ventricle and right ventricle functions, the method can then be accomplished according to Step 2 described below.

Step 2: Examination of left ventricle and right ventricle functions

If no pathology has been revealed in the peripheral circulation, the parameters (such as the Stroke Volume (SV) and the Index Balance (IB)), for the systemic circulation, and the ones for the pulmonary circulation, may be compared in order to define whether there is any pathology in the left or right ventricle's functions. This is based on the fact that various heart pathologies cause redistribution of the blood between the systemic and the pulmonary circulatory systems.

In general, when the value of SV measured in the *"arm–arm"* placement is substantially equal to that measured by the *"arm–leg"* placement, functions of the left and right heart ventricles are considered to be in order. Imbalances may be caused by various reasons and can be classified as is suggested below.

For example, a temporary imbalance occurs whenever the right ventricle pumps more blood into the pulmonary blood vessels, than is removed therefrom by the left ventricle. Such a situation is a signal of the left ventricle heart failure (LVHF), which may be caused by various reasons, such as: impairment in the filling of the left ventricle (as in mitral stenosis); inability of the left ventricle to adequately empty itself during each contraction (as in heart failure caused by hypertension, coronary artery disease, aortic insufficiency or aortic stenosis, etc.). The excess blood may accumulate in the lungs even when the output of the left ventricle is normal or increased, but it is lagging behind that of the right ventricle, i.e. the left ventricle is unable to sufficiently increase its output to clear the lungs. Such a case may occur when a patient suffers from fever, anemia, beriberi, thyrotoxicosis, etc., where normal function of the left ventricle is impared by the desease.

It is understood that if the SV value measured by the *"arm–leg"* electrode's placement (and predominantly characterizing functions of the left ventricle) is substantially less than the normal known SV value for the left ventricle, it indicates the left vetricle heart failure (LVHF). Moreover, when the SV value measured by the *"arm–leg"* electrode's placement (and predominantly characterizing functions of the left ventricle) is substantially lower than the SV value measured by the *"arm–arm"* electrodes placement, this may be an indication of at least one of the following:

1. Where such a discrepancy is additionally accomplished by increasing (above normal) of the IB parameter characterizing volume of the extracellular fluids in the individual's body, this may be an indication of a lung edema. Thereby, it is often possible to early diagnose a lung edema.
2. Where the IB value is normal, the discrepancy may be indicative of the existence of disturbances in the lung blood circulation.

In accordance with the most preferred embodiment of the above described method of examination of left ventricle and right ventricle functions, the SV and the IB parameters are calculated according to the semi–empiric formulae given in the specification.

According to a second aspect of the invention, there is provided a non–invasive medical device for accurately determining at least one cardiorespiratory parameter of the human body, said device comprising:

at least two electrodes,

electrical body integral bioimpedance measuring unit coupled to the electrodes and including a high stability amplitude alternative current source and an electronic circuit for automatic derivation of an active component of said integral bioimpedance; and

a computer coupled to the electrical integral bioimpedance measuring unit and to a display means for calculating and displaying said at least one cardiorespiratory parameter from the active component of the integral bioimpedance.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how the same may be carried out in practice, some preferred embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 is a representation of a number of cardiac cycles during a respiratory cycle and the corresponding electrocardiography (ECG) measurement for illustrating the averaging method according to the invention;

Fig. 2A is a block diagram showing functionally a measuring system according to the invention using two electrodes applied to an individual's one arm and one leg, respectively;

Fig. 2B is a schematic circuit diagram representing the system shown in Fig. 2A;

Figs. 2C, 2D and 2E depict bipolar and tetrapolar modifications of the system shown in Fig. 2A;

Fig. 2F illustrates a measuring system using two (or four) electrodes applied to two arms of the individual;

Fig. 2G illustrates a measuring system using two (or four) electrodes applied to the individual's legs;

Fig. 2H illustrates the best mode of electrodes' placement suitable both for obtaining the main cardiorespiratory parameters according to the invention, and for diagnosing disturbances in the heart right and left ventricle functions and in the peripheral blood circulation;

Fig. 3 is a block diagram showing one embodiment of an electrical bioimpedance measuring system according to the invention; and

Figs. 4A and 4B are a flow chart showing the principal steps in a method for using the measuring system according to the invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Fig. 1 illustrates two curves. The lower curve 2 is a superposition of two curves, a curve 4 reflecting resistive changes of the bioimpedance caused by the respiration process, and another curve (not shown alone) representing resistive changes of the bioimpdance resulting from the cariac cycles. The upper curve 6 is an ECG curve. The ECG curve may serve for the synchronization of the bioimpedance measurement, namely it defines time boundaries of cardiac cycles. For calculation of a cardiorespiratory parameter according to the mentioned semi-empiric formulae, a number of readings of the parameter must be obtained for a number of cardiac cycles during a single respiratory cycle (for example, three readings in the specific illustrative example of curve 2), and then an average of the measured readings is to be defined. The readings may be obtained during more than one respiratory cycle. Some of the parameters (δr, α, β) used in the semi-empiric formula (1) are shown in Fig. 1.

Figs. 2A and 2B show respectively a block-diagram of a non-invasive two-electrode system for automatic express determination of the main cardiorespiratory parameters of a patient **10** and an equivalent electrical circuit diagram of the patient **10**.

Two electrodes **11** are applied to the distal parts of one arm and one leg of the individual. A first electrode **11a** is connected to the distal part of the left arm, and a second electrode **11b** to the distal part of the patient's right leg. An electrical integral bioimpedance measuring unit **12** delivers a high stability amplitude alternating current through a single channel **13**, via the electrodes **11** to the individual **10**. The integral impedance curve of the individual **10** is obtained from the same electrodes **11** and is transferred through the same single channel **13** to the measuring unit **12**, which converts the integral impedance curve. The converted working signal is then transferred through a second single channel **14** to a computer **15**, where cardiorespiratory parameters of the whole body and parameters concerning extracellular fluids of the whole body are calculated using empiric formulae.

Personal data characteristic of the individual **10** which is entered into the computer **15** via a keyboard (not shown) can also be taken into account when calculating the cardiorespiratory parameters. Typically, the personal data includes height, weight, age, sex, results of a blood test, identification index, etc. An output signal **14** from the electrical integral bioimpedance measuring unit **12** is fed to the computer **15** and stored in an internal table. Preliminary processing of the raw data is performed so as to derive a plethysmographic and rheographic curve, on the basis of which the respiratory cycle and heart beat complex indices (marks) are determined (the beginning of the anacrotic slope, the length of heart complexes' cycle, their maximum amplitude, e.g. by locating extremes of the curves, etc.) (see Fig.1). The area section under the initial impedance curve reflecting the phases of the fast and slow ejection of the blood during a cardiocycle is used for computing the main parameters. Based on this data and the individual's personal data, the parameters are determined using empiric formulae, such as those described in the present specification.

The computer **15** may be programmed to calculate a plurality of parameters based on the above definition of the Stroke Volume equation **(1)**.

Some other possible variants of the electrodes configurations are shown in Figs. 2C to 2G. In each case, either two or four electrodes may be connected to the patient. In case of the former, the arrangement reduces to the bipolar system described above with reference to Figs. 2A and 2B of the drawings. If the electrodes which are shown by dotted lines are also connected, then the arrangement yields a tetrapolar scheme in which two of the electrodes are active in injecting the current, whilst two of the electrodes are passive and measure the resultant signal.

Calculation of the cardiovascular parameters in this configuration needs specific corrections in comparison with hitherto–proposed calculations for the four–electrode system. These corrections may require means of adjusting of the empiric coefficients as defined above.

Reference is now made to Fig. 2H illustrating the best mode of electrodes' placement suitable both for obtaining the main cardiorespiratory

parameters according to the invention, and for diagnosing of disturbances in the heart right and left ventricle functions and in the periphery blood circulation.

To the distal parts of all the individual's two arms and two legs, four electrodes are attached which are marked *"a"* in the figure, for measurement by the bipolar mode. Another pair of current injecting electrodes, marked *"b"*, are attached to one arm and one leg of the individual, typically the right arm and the right leg. These electrodes which are preferably placed, as shown in the figure, in a more peripheral position than the *"a"* electrodes, are used to measure the skin resistance, R_s, by the combined bipolar/tetrapolar mode described above. Four additional and optional electrodes, marked *"c"* are attached to the shoulders and to the hips of the individual, which are used for the purpose of obtaining information on the peripheral circulation, the blood circulation in the arms and legs. This electrode configuration thus allows derivation of a complete set of cardiorespiratory parameters, as described above, and also functional circulatory parameters, distribution of the extracellular fluid throughout the body, and diagnosis of disturbances in the blood circulation and in the heart right and left ventricle functions.

In addition to the units 12 and 15 mentioned in the description of Fig. 2A, there is introduced a multiplexer 16 enabling to perform a so-called multi-channel measurement. Such a multi-channel mode allows, for example, to select a preferred electrode attachment for further bioimpedance measurements on the body of the individual.

Fig. 3 is a block-diagram of an electrical bioimpedance measuring system 60 according to the invention. The Bioimpedance Measuring Unit is unit **61** in the drawing. It should be noted, that though two electrodes **62** and **63** are shown applied to the patient's arm and leg, according to the invention they may be applied to any two patient's extremities, and the block diagram may comprise a multiplexer, as shown in Fig. 2H. Two additional ECG electrodes are applied to the arms of the patient and connected to an ECG measurement circuit **64**.

A micro-controller **65** (such as model 80196KC manufactured by Intel®) combining the functions of the A/D converter and a microprocessor, is provided for processing in real time a curve obtained from the ECG circuit **64**, together with the curve obtained from the Bioimpedance Measuring Unit **61** and being a composition of a direct "R" and an alternating "δr" components of an active bioimpedance component. Additionally, the micro-controller **65** receives the initial complete bioimpedance curve from the Bioimpedance Measuring Unit 61. When processing both the initial bioimpedance curve and the curve of the active bioimpedance component, the micro-controller **65** and a computer **66** (such as a note-book computer) continuously calculate a capacitance of the electric circuit of the human body. It should be clarified that, from the electric point of view, the human body behaves as an RC (resistance-capacitance) impedance. The value of the capacitance of the human body can be calculated by the formula:

$$Z = R - \frac{j}{\omega C}$$

and continuously checked.

An excess of the capacitance over a predetermined threshold, or oscillation of the capacitance indicates degradation of the contacts between the electrodes and the patient's skin. In such case, an appropriate alarm is activated under control of the computer **66**. The outputs of the micro-controller **65** are connected to the computer **66** via isolation circuits **67** (such as opto-isolators MOC 8080, Motorola®) providing electrical protection of the patient from a random voltage, via a correction circuit **68** (such as the driver RS232C) and an appropriate RS232C cable **69**. The correction circuit **68** and the micro-controller **65** are supplied with electrical voltage of +5V from the computer **66**. The voltage ±5V from the power supply **70** is converted to +5V by a DC/DC converter **71**. The DC/DC converter **71** also performs a function of an isolation circuit. The power supply unit **70** provides the blocks of the instrument **60** with electrical power of ± 5V.

Figs. 4A and 4B shows a flow chart diagram of an algorithm of measuring of the main cardiorespiratory parameters in accordance with which the system functions.

At step 98 the system is switched on, and, if the measurements are provided via a multiplexer, one channel (i.e. a specific electrode attachment) is selected for the bioimpedance measurements on the individual's body. Such a channel is chosen after performing a number of preliminary measurements via different electrode attachments, and each os such measurements actually are made according to the flow chart which is described later on. Step 98 allows to chose a pair of healthy extremities for the main session of the measurements and provides information which may be useful for diagnostic purposes.

At step 100 the duration of the monitoring session is chosen. The duration of the monitoring session can be defined as a duration of an initial bioimpedance curve section intended for an averaged calculation of the necessary parameters, and can be chosen in the range of about 10 to 30 sec.

At step 102 a check is performed in order to determine whether the information from the Bioimpedance Measurement Unit 61 is obtained on the display. If not, the reason should be detected and indicated by at least one of the following test blocks:

Block 104 The impedance between electrodes and the skin is not stable;

Block 106 There is no contact in the cable RS232C;

Block 108 The ECG electrodes contact is poor;

Block 110 A poor contact of the bioimpedance measuring electrodes.

After overcoming the reason for the malfunction, the cycle should be started again (returning to step 102). If no exit command were keyed by an operator (block 112), the digital test readings of R (active impedance), C (capacitance), and Z (complete impedance) will be displayed in real time on the display (step 114).

When these parameters are stabilized (step 116), the next procedure is started wherein the QRS pulse is derived from the ECG curve (step 118) for marking the bioimpedance curve.

Step 120 represents the processes of marking of the bioimpedance curve by the marks obtained at step 118, further processing of the rheographic information and computing the main cardiorespiratory parameters being based on the average data obtained during a respiration cycle.

If a record of the computed parameters is not aborted at step 122, the parameters should be stored in the computer. The parameters in the system can be computed either in a regime of a single measurement (step 124), or in a continuous regime (step 126).

The computed parameters may be stored in the computer in one of the following two ways: the values of the parameters can be either entered into a data base of the patient in the computer (step 132), or the parameters can be written down as a temporary protocol in the computer (step 134). At step 130 it is decided whether or not the data base should be used for the record of the computed parameters.

When the single monitoring session is finished, a plurality of the computed parameters are indicated on the display (step 136). At step 138 there is defined whether or not to repeat the measurements. The order to repeat the measurements can be entered either manually by the operator, or automatically, if the continuous regime were chosen. If such an order is received, another monitoring session will be started, and additional readings of the parameters will be recorded. If the measurements are not to be repeated, the process will be stopped at step 140.

It has been shown that the method according to the invention comprises applying the electrodes according to either a bipolar or tetrapolar system. In either case, a preliminary connection of four electrodes may be effected to the respective distal parts of the human extremities, whereafter the integral impedance is preliminarily measured between each pair of electrodes placed on each arm and leg. Determination of the main

cardiorespiratory parameters of the human body is made in accordance with which pair of electrodes is characterized by the lowest integral impedance.

In accordance with one embodiment, the method according to the invention further includes a computerized calculation of parameters concerning extracellular fluids of the patient's body, the calculations being based on measurements accomplished at two different current frequencies.

It should further be noted that the method according to one aspect of the invention may be employed for diagnosing some cardiorespiratory and blood cifculation diseases, for example for revealing the pathological extremities, where arterial blood circulation defects occur or another pathological defect takes place.

Moreover, if both of the upper (or both of the lower) extremities are under treatment or have associated therewith pathological defects (thrombophlebitis, tremor, oedema), or if the patient needs to be monitored for a long period of time, or has to have his arms (legs) free for other types of treatment or for required physical exercises, other arrangements of the electrodes' connection can be effected.

In the preferred embodiment a plurality of such parameters are calculated by said method, including hemodynamic parameters such as Stroke Volume, Systolic Index, Pulse Rate, Cardiac Output, Heart Index, Reserve Index, Total Resistance Index, Index of Tone Stabilization; and respiratory parameters such as Rate of Respiration, Index of Respiration changes, Index of Respiration Intensiveness, Index of Hemodynamic Security; and additional parameters, such as Index of Respiratory Duration and Index of Tidal Respiratory Volume.

In yet a further embodiment, a plurality of parameters characterizing extracellular fluids of the human body are calculated, such as Volume of Extracellular Fluids of the whole patient's body and Index of Fluid Balance of the whole body.

While the present invention has been described with the reference to the attached drawings, it should be appreciated, that other embodiments

of the described system and its elements can be suggested and should be considered as part of the invention.

CLAIMS:

1. A method for determining at least one main cardiorespiratory parameter of an individual, comprising the steps of:

attaching at least two electrodes to the body of an individual and providing a low impedance contact between the electrodes and a skin of the individual, and positioning the electrodes on at least one arm or at least one leg and at least another arm or at least another leg of the individual to enable current to pass between said at least two electrodes on said at least one arm or at least one leg to at least another arm or at least another leg of the individual;

passing an alternating current with a stable and constant amplitude through said at least two electrodes,

measuring, while passing said alternating current, a potential change as the result of the current flow to obtain a measurement of an electrical bioimpedance of the body of the individual from a measured potential between the said at least two electrodes;

simultaneously separating an active component of the integral bioimpedance from measured said bioimpedance;

calculating the at least one of a cardio parameter and a respiratory parameter of the individual from the active component of said bioimpedance, using a semi-empiric formula applicable to integral bioimpedance measurements to obtain a number of values of said at least one parameter for a number of cardiac cycles during a respiratory cycle, and calculating an average of said at least one parameter during a single respiratory cycle; and

displaying said average of said at least one parameter thus obtained.

2. The method according to claim 1, wherein said cardiac parameter comprises a Stroke Volume (SV) parameter calculated substantially according to the following semi-empiric formula applicable to integral bioimpedance measurements:

$$SV = \frac{Hct_{corr.}}{K(shape*sex*age)} * \delta r \frac{H^2_{corr.}}{R} * \frac{\alpha + \beta}{\beta} * Kel * Kw * IB$$

where:

$Hct_{corr.}$ is a correcting factor depending from hematocrit, being 145 + 0.35(Hct – 40);

Hct is the hematocrit, obtained from analysis of the individual's blood;

$K(shape*sex*age)$ is a coefficient of the individual's body, being:

527.3 –(3.1 * (Actual Age –20)), for men younger than 20 years old;

527.3, for men from 20 to 40 years old;

527.3 + (3.1 * (Actual Age –40)), for men older than 40 years old;

587.6 –(2.9 * (Actual Age –18)), for women younger than 18 years old;

587.6, for women from 18 to 50 years old;

587.6 + (2.9 * (Actual Age –50)), for women older than 50 years old;

δr is the amplitude value of the change of the individual's basic body resistance R at the anacrotic (systolic) portion of a cardiac cycle;

R is the individual average basic body resistance during one cardiac cycle;

$H_{corr.}$ is a corrected height of the individual, given by:

$$H_{corr} = (H_{real} + 2) \quad \text{if} \quad \frac{\text{legs length}}{\text{body length}} = 0.66 \pm 0.04$$

or

$$H_{corr} = (H_{real} - 2) \quad \text{if} \quad \frac{\text{legs length}}{\text{body length}} = 0.54 \pm 0.04$$

or

$$H_{corr} = (H_{real}) \quad \text{if} \quad 0.62 \geq \frac{\text{legs length}}{\text{body length}} \geq 0.58$$

$\alpha + \beta$ is duration of a cardiac cycle, being a sum of its anacrotic and catacrotic portion;

β is duration of the catacrotic portion of a cardiac cycle;

Kel is a coefficient depending on ion concentration in the individual's blood plasma, calculated based on the blood analysis and being given by:

a) for an individual exposed to a hemodialysis

Kel = sum of the blood concentrations at $\frac{Na^{+}+K^{+}+Mg^{+}+Ca^{+}}{142+13}$

b) for other individuals

Kel = blood concentration of $\frac{Na^{+}}{142}$;

K_w is a weight coefficient, being a ratio $\frac{Actual\ weight}{Ideal\ weight}$, where Ideal weight being obtained from International Tables of ideal weights;

IB is an Index Balance, reflecting ratio between the measured volume of extracellular fluids and the individual's proper volume of extracellular fluids.

3. A method according to Claim 2, wherein the Index Balance is calculated based on the following formula:

$$\frac{R_{ind.prop}}{R_{measured}}$$

where *R measured* is the measured resistive component of the individual's bioimpedance, not including the individual's skin resistance;

$R_{ind.\ prop.}$ is a proper value of the resistive component of the indivudual's bioimpedance being calculated according to the two following formulae:

$$\frac{0.42H^2}{0.47W - 8.30} \quad \text{for men}$$

$$\frac{0.42\ H^2}{0.37\ W - 4.96} \quad \text{for women}$$

where H is the individual's height, and

W is the individual's actual weight.

4. The method according to claim 1, comprising attaching the electrodes to distal parts of the individual's arms and legs.

5. The method in accordance with claim 1, wherein the method is carried out in a bipolar mode, and said attaching step comprises attaching at least two electrodes to the body of the individual with each electrode being used both for said passing current and said measuring step.

6. The method in accordance with claim 1, carried out in a tetrapolar mode, and said attaching step comprises attaching at least four electrodes to the body of the individual, of which at least two electrodes are used for said passing current step, and at least two other different electrodes are used for said measuring step.

7. A method according to Claim 6, comprising attaching two electrodes to one arm or leg and two electrodes to another arm or leg, passing the current between a first pair of electrodes, each electrode of the pair being located on a different arm or leg and measuring the potential between a second pair of electrodes, different than the first.

8. The method according to Claim 1, wherein said attaching step comprises:

attaching first basic pair of electrodes to the individual, by attaching one electrode of said pair on one arm or leg and another electrode of said pair on another arm or leg;

attaching a pair of auxiliary electrodes by attaching each auxiliary electrode to one of the arms or legs to which the basic pair of electrodes are attached and positioning the auxiliary electrodes on a more distal portion of the arms or legs than the basic pair;

said measuring step comprises:

measuring impedance comprising a first step in which current is passed and potential is measured using the basic pair of electrodes, and a second step wherein current is passed through the auxiliary electrodes and potential measured through the basic electrodes, in a tetrapolar measurement mode;

calculating the difference between the potential measured in the first step and the potential measured in the second step to calculate resistance of the skin of the individual from said difference;

continuously reducing the resistance of the skin of the individual from a value of said active component of the bioimpedance of the individual.

9. A method according to claim 3, further comprising a preliminary step of examination of the peripheral blood circulation of the individual, said preliminary step including:

measuring at least one of parameters P, P_1, P_2 or P_3 between an individual's two arms having an *"arm–arm"* electrode attachment, between the individual's arm and leg having an *"arm–leg"* electrode attachment, and between the individual's two legs having a *"leg–leg"* electrode attachment; said parameters being calculated substantially by the following formulae:

$$P = \delta r \frac{H^2 corr}{R\ measured} * \frac{\alpha + \beta}{\beta}$$

$$P_1 = \frac{\delta r}{R\ measured}$$

$$P_2 = \frac{H^2 corr}{R\ measured}$$

$$P_3 = \frac{\alpha + \beta}{\beta}$$

wherein *R measured* is as defined in Claim 3, and δr, H, α and β are as defined in Claim 2;

comparing readings obtained in said *"leg–leg"* electrode attachment to the readings obtained in said *"arm–arm"* and said *"arm–leg"* electrode attachment, and

diagnosing peripheral circulatory disturbances at least in one of the individual's legs based on difference in readings obtained in the *"leg–leg"* electrode attachment compared to other attachments.

10. The method according to claim 9, wherein said preliminary step of examination of the peripheral blood circulation comprises:

applying a pair of additional electrodes to hips of the individual,

providing measurements of at least one of the parameters P, P_1 or P_2 between a distal part of each leg and a corresponding hip;

obtaining for each leg values of proper parameters P_{proper} , $P_{1prop.}$ or $P_{2prop.}$ for the individual, calculated according to the following formulae:

$$P_{prop} = \delta \frac{H^2 corr}{R_{ind.prop}} * \frac{\alpha + \beta}{\beta}$$

$$P_{1prop} = \frac{\delta r}{R_{ind.prop}}$$

$$P_{2prop} = \frac{H^2 corr}{R_{ind.prop}}$$

wherein $R_{ind.\ prop.}$ is as defined in Claim 3;

comparing the readings of at least one of the parameters P, P_1 or P_2 with the readings of the proper parameters P_{prop}, $P_{1\ prop}$ or $P_{2\ prop}$ for each leg, respectively,

and defining a pathologic leg if the readings related to a leg substantially differ from the proper parameters, and excluding said pathologic leg from the electrodes attachment chosen for determining the main cardiorespiratory parameters.

11. The method according to Claim 3, comprising applying four additional electrodes, one to each of shoulders and hips of the individual, and a preliminary step of revealing disturbances in a peripheral blood circulation of the individual; said preliminary step including determining of at least one of parameters P, P_1, or P_2 between the distal part of each of the

arms and legs and the corresponding additional electrode; said parameters being calculated substantially by the following formulae:

$$P = \delta r \frac{H^2 corr}{R\ measured} * \frac{\alpha + \beta}{\beta}$$

$$P_1 = \frac{\delta r}{R\ measured}$$

$$P_2 = \frac{H^2 corr}{R\ measured}$$

wherein *R measured* is as defined in Claim 5 and δr, H, are as defined in Claim 4;

obtaining for each arm and leg values of the individual's proper parameters P_{prop}, P_{1prop} or P_{2prop}, the values calculated substantially according to the following formulae:

$$P_{prop} = \delta \frac{H^2 corr}{R_{ind.prop}} * \frac{\alpha + \beta}{\beta}$$

$$P_{1prop} = \frac{\delta r}{R_{ind.prop}}$$

$$P_{2prop} = \frac{H^2 corr}{R_{ind.prop}}$$

wherein $R_{ind.\ prop.}$ is as defined in Claim 5;

comparing at least one of the parameters P, P_1 or P_2 with a corresponding proper parameter P_{prop}, $P_{1\ prop}$ or $P_{2\ prop}$ for each arm and leg;

and defining at least one pathologic arm or leg if the readings of the parameters P, P_1 or P_2 related to said at least one arm or leg substantially differ from the values of the corresponding proper parameters P_{prop}, $P_{1\ prop}$ or $P_{2\ prop}$, and excluding said at least one pathologic arm or leg from the

electrode attachment chosen for determining the main cardiorespiratory parameters.

12. The method according to Claim 10, wherein the Stroke Volume (SV) parameter is measured both for an *"arm–arm"* electrode attachment, and for an *"arm–leg"* electrodes attachment, the two arms and the leg chosen for measurement having no disturbance in blood circulation; and wherein the two measurements are compared to each other;

and wherein a left ventricle heart failure is diagnosed where the SV value measured in the *"arm–arm"* electrodes attachment substantially exceeds the SV value measured in the *"arm–leg"* electrode attachment.

13. The method according to claim 11, said step of measuring the Stroke Volume (SV) parameter including measuring the Stroke Volume (SV) both for the *"arm–arm"* electrode attachment, and for the *"arm–leg"* electrode attachment, the two arms and the leg chosen for measurement having no disturbance in blood circulation; comparing the two measurements to each other; and wherein

a left ventricle heart failure is diagnosed where the SV value measured in the *"arm–arm"* electrode aattachment substantially exceeds the SV value measured in the *"arm–leg"* electrode attachment.

14. The method according to Claim 12, further comprising measuring of the Index Balance (IB) parameter;

diagnosing lung edema where the SV value measured in the *"arm–arm"* electrode attachment substantially differs from the SV value measured in the *"arm–leg"* electrode attachment, and the IB parameter is substantially higher than 1; and

diagnosing problems in lung blood circulation where the SV value measured in the *"arm–arm"* electrode attachment substantially exceeds the SV value measured in the *"arm–leg"* electrode attachment, and the IB equals about 1.

15. A method of diagnosing malfunctions in peripheral blood circulation of an individual, comprising:

attaching at least four electrodes to the body of an individual and providing a low impedance contact between the electrodes and a skin of the individual, and positioning the electrodes on the individual's arms and legs so as to arrange a first pair of the electrodes applied to the individual's two arms and forming a so–called *"arm–arm"* electrode attachment, a second pair of the electrodes applied to the individual's two legs and forming a so–called *"leg–leg"* electrode attachment, and a third pair of the electrodes applied to a leg and an arm of the individual and forming a so–called *"arm–leg"* electrode attachment;

passing an alternating current with a stable and constant amplitude through each of said pairs of the electrodes in sequence,

measuring, while passing said alternating current, a potential change as the result of the current flow to obtain a measurement of an electrical bioimpedance of the body of the individual from a measured potential corresponding to each of said electrode attachments in sequence;

separating an active component of the bioimpedance from measured said bioimpedance during each of the measurements;

measuring at least one of parameters P, P_1, P_2, or P_3 and cardiorespiratory parameter of the individual for each of the electrode attachments, said parameters being calculated substantially by the following formulae, the calculations being accomplished based on the average data obtained during a respiration cycle:

$$P = \delta r \frac{H^2 corr}{R\ measured} * \frac{\alpha + \beta}{\beta}$$

$$P_1 = \frac{\delta r}{R\ measured}$$

$$P_2 = \frac{H^2 corr}{R\ measured}$$

$$P_3 = \frac{\alpha + \beta}{\beta}$$

where *R measured* is the measured resistive component of the individual's bioimpedance, not including the individual's skin resistance;

δr is the amplitude value of the change of the individual's basic body resistance R at the anacrotic (systolic) portion of a cardiac cycle;

$H_{corr.}$ is a corrected height of the individual, given by:

$$H_{corr} = (H_{real} + 2) \quad \text{if} \quad \frac{\text{legs length}}{\text{body length}} = 0.66 \pm 0.04$$

or

$$H_{corr} = (H_{real} - 2) \quad \text{if} \quad \frac{\text{legs length}}{\text{body length}} = 0.54 \pm 0.04$$

or

$$H_{corr} = (H_{real}) \quad \text{if} \quad 0.62 \geq \frac{\text{legs length}}{\text{body length}} \geq 0.58$$

$\alpha + \beta$ is duration of a cardiac cycle, being a sum of its anacrotic and catacrotic portion;

β is duration of the catacrotic portion of a cardiac cycle;

comparing readings obtained in said *"leg–leg"* electrode attachment to the readings obtained in said *"arm–arm"* and said *"arm–leg"* electrode attachment, and

diagnosing peripheral circulatory disturbances at least in one of the individual's legs based on difference in readings obtained in the *"leg–leg"* electrode attachment compared to other attachments.

16. The method according to claim 15, further comprising:

applying a pair of additional electrodes to hips of the individual,

providing measurements of at least one of the parameters P, P_1 or P_2 between a distal part of each leg and a corresponding hip;

obtaining for each leg values of proper parameters P_{proper} , $P_{1prop.}$ or $P_{2prop.}$ for the individual, calculated according to the following formulae:

$$P_{prop} = \delta \frac{H^2 corr}{R_{ind.prop}} * \frac{\alpha + \beta}{\beta}$$

$$P_{1prop} = \frac{\delta r}{R_{ind.prop}}$$

$$P_{2prop} = \frac{H^2 corr}{R_{ind.prop}}$$

wherein $R_{ind.\ prop.}$ is a proper value of the resistive component of the indivudual's bioimpedance being calculated according to the two following formulae:

$$\frac{0.42 H^2}{0.47 W - 8.30} \quad \text{for men}$$

$$\frac{0.42\ H^2}{0.37\ W - 4.96} \quad \text{for women}$$

where H is the individual's height, and

W is the individual's actual weight;

comparing the readings of at least one of the parameters P, P_1 or P_2 with the readings of the proper parameters P_{prop}, $P_{1\ prop}$ or $P_{2\ prop}$ for each leg, respectively,

and defining a pathologic leg if the readings related to a leg substantially differ from the proper parameters.

17. A method of diagnosing malfunctions in peripheral blood circulation of an individual, comprising:

attaching four main electrodes to the distal parts of each of the individual's arms and legs and providing a low impedance contact between the electrodes and a skin of the individual;

applying four additional electrodes, one to each of shoulders and hips of the individual;

passing an alternating current with a stable and constant amplitude via each arm and leg in sequence, between a main electrode and an additional electrode positioned on the same said arm or leg,

measuring, while passing said alternating current, a potential change as the result of the current flow to obtain a measurement of an electrical bioimpedance of the corresponding arm or leg;

separating an active component of the bioimpedance from measured said bioimpedance during each of the measurements;

determining of at least one of parameters P, P_1, or P_2 between the distal part of each of the arms and legs and the corresponding additional electrode; said parameters being calculated substantially by the following formulae, the calculations being accomplished based on the average data obtained during a respiration cycle:

$$P = \delta r \frac{H^2 corr}{R\ measured} * \frac{\alpha + \beta}{\beta}$$

$$P_1 = \frac{\delta r}{R\ measured}$$

$$P_2 = \frac{H^2 corr}{R\ measured}$$

where *R measured* is the measured resistive component of the individual's bioimpedance, not including the individual's skin resistance;

δr is the amplitude value of the change of the individual's basic body resistance R at the anacrotic (systolic) portion of a cardiac cycle;

$H_{corr.}$ is a corrected height of the individual, given by:

$$H_{corr} = (H_{real} + 2) \quad \text{if} \quad \frac{\text{legs length}}{\text{body length}} = 0.66 \pm 0.04$$

or

$$H_{corr} = (H_{real} - 2) \quad \text{if} \quad \frac{\text{legs length}}{\text{body length}} = 0.54 \pm 0.04$$

or

$$H_{corr} = (H_{real}) \quad \text{if} \quad 0.62 \geq \frac{\text{legs length}}{\text{body length}} \geq 0.58$$

$\alpha + \beta$ is duration of a cardiac cycle, being a sum of its anacrotic and catacrotic portion;

β is duration of the catacrotic portion of a cardiac cycle;

obtaining for each arm and leg values of the individual's proper parameters P_{prop}, P_{1prop} or P_{2prop}, the values being calculated substantially according to the following formulae:

$$P_{prop} = \delta \frac{H^2 corr}{R_{ind.prop}} * \frac{\alpha + \beta}{\beta}$$

$$P_{1prop} = \frac{\delta r}{R_{ind.prop}}$$

$$P_{2prop} = \frac{H^2 corr}{R_{ind.prop}}$$

wherein $R_{ind.\ prop.}$ is a proper value of the resistive component of the indivudual's bioimpedance being calculated according to the two following formulae:

$$\frac{0.42 H^2}{0.47 W - 8.30} \quad \text{for men}$$

$$\frac{0.42\ H^2}{0.37\ W - 4.96} \quad \text{for women}$$

where H is the individual's height, and

W is the individual's actual weight;

comparing at least one of the parameters P, P_1 or P_2 with a corresponding proper parameter P_{prop}, $P_{1\ prop}$ or $P_{2\ prop}$ for each arm and leg;

and defining at least one pathologic arm or leg if the readings of the parameters P, P_1 or P_2 related to said at least one arm or leg substantially differ from the values of the corresponding proper parameters P_{prop}, $P_{1\ prop}$ or $P_{2\ prop}$.

18. A method of diagnosing malfunctions in peripheral blood circulation in an arm or leg of an individual, comprising:

attaching one main electrode to the distal part of one arm or leg of the individual, one additional electrode to the shoulder or hip of same said arm or leg of the individual, and providing a low impedance contact between said two electrodes and a skin of the individual;

passing an alternating current with a stable and constant amplitude via said arm or leg, between the main electrode and the additional electrode,

measuring, while passing said alternating current, a potential change as the result of the current flow to obtain a measurement of an electrical bioimpedance of said arm or leg;

separating an active component of the bioimpedance from measured said bioimpedance during the measurement;

determining of at least one of parameters P, P_1, or P_2 ; said parameters being calculated substantially by the following formulae, the calculations being accomplished based on the average data obtained during a respiration cycle:

$$P = \delta r \frac{H^2 corr}{R\ measured} * \frac{\alpha + \beta}{\beta}$$

$$P_1 = \frac{\delta r}{R\ measured}$$

$$P_2 = \frac{H^2 corr}{R\ measured}$$

where *R measured* is the measured resistive component of the individual's bioimpedance, not including the individual's skin resistance;

δr is the amplitude value of the change of the individual's basic body resistance R at the anacrotic (systolic) portion of a cardiac cycle;

$H_{corr.}$ is a corrected height of the individual, given by:

$$H_{corr} = (H_{real} + 2) \quad \text{if} \quad \frac{\text{legs length}}{\text{body length}} = 0.66 \pm 0.04$$

or

$$H_{corr} = (H_{real} - 2) \quad \text{if} \quad \frac{\text{legs length}}{\text{body length}} = 0.54 \pm 0.04$$

or

$$H_{corr} = (H_{real}) \quad \text{if} \quad 0.62 \geq \frac{\text{legs length}}{\text{body length}} \geq 0.58$$

$\alpha + \beta$ is duration of a cardiac cycle, being a sum of its anacrotic and catacrotic portion;

β is duration of the catacrotic portion of a cardiac cycle;

obtaining for same said arm or leg values of the individual's proper parameters P_{prop}, P_{1prop} or P_{2prop}, the values being calculated substantially according to the following formulae:

$$P_{prop} = \delta \frac{H^2 corr}{R_{ind.prop}} * \frac{\alpha + \beta}{\beta}$$

$$P_{1prop} = \frac{\delta r}{R_{ind.prop}}$$

$$P_{2prop} = \frac{H^2 corr}{R_{ind.prop}}$$

wherein $R_{ind.\ prop.}$ is a proper value of the resistive component of the indivudual's bioimpedance being calculated according to the two following formulae:

$$\frac{0.42H^2}{0.47W - 8.30} \quad \text{for men}$$

$$\frac{0.42\ H^2}{0.37\ W - 4.96} \quad \text{for women}$$

where H is the individual's height, and

W is the individual's actual weight;

comparing at least one of the parameters P, P_1 or P_2 with a corresponding proper parameter P_{prop}, $P_{1\ prop}$ or $P_{2\ prop}$ for said arm or leg;

diagnosing a malfunction in blood circulation in said arm or leg of the individual if the readings of the parameters P, P_1 or P_2 substantially differ from the values of the corresponding proper parameters P_{prop}, $P_{1\ prop}$ or $P_{2\ prop}$.

19. A method of diagnosing cardiorespiratory diseases of an individual, comprising:

attaching at least three electrodes to the body of an individual and providing a low impedance contact between the electrodes and a skin of the individual, and positioning the electrodes on the individual's arms and legs so as to arrange a first pair of the electrodes applied to the individual's two arms and forming a so-called *"arm-arm"* electrode attachment, and a second pair of the electrodes applied to a leg and an arm of the individual and forming a so-called *"arm-leg"* electrode attachment, the two arms and the leg chosen for measurement having no disturbance in blood circulation;

passing an alternating current with a stable and constant amplitude through each of said pairs of the electrodes in sequence,

measuring, while passing said alternating current, a potential change as the result of the current flow to obtain a measurement of an electrical bioimpedance of the body of the individual from a measured potential corresponding to each of said electrode attachments in sequence;

separating an active component of the bioimpedance from measured said bioimpedance during each of the measurements;

measuring the Stroke Volume (SV) parameter of the individual both for the *"arm–arm"* electrode attachment, and for the *"arm–leg"* electrodes attachment from the active component of said respective bioimpedance measurement, using a semi-empiric formula applicable to integral bioimpedance measurements, the calculations being accomplished based on the average data obtained during a respiration cycle;

comparing the two measurements of the SV parameters to each other;

diagnosing a left ventricle heart failure where the SV value measured in the *"arm–arm"* electrodes attachment substantially exceeds the SV value measured in the *"arm–leg"* electrode attachment.

20. The method according to Claim 19, further comprising measuring of an Index Balance (IB) parameter reflecting ratio between the measured volume of extracellular fluids and the individual's proper volume of extracellular fluids;

diagnosing lung edema where the SV value measured in the *"arm–arm"* electrode attachment substantially differs from the SV value measured in the *"arm–leg"* electrode attachment, and the IB parameter is substantially higher than 1; and

diagnosing problems in lung blood circulation where the SV value measured in the *"arm–arm"* electrode attachment substantially exceeds the SV value measured in the *"arm–leg"* electrode attachment, and the IB equals about 1.

21. The method according to claim 20, wherein the Stroke Volume (SV) parameter is calculated substantially according to the following semi-empiric formula applicable to integral bioimpedance measurements:

$$SV = \frac{Hct_{corr.}}{K(shape*sex*age)} * \delta r \frac{H^2_{corr.}}{R} * \frac{\alpha + \beta}{\beta} * Kel * Kw * IB$$

where:

$Hct_{corr.}$ is a correcting factor depending from hematocrit, being $145 + 0.35(Hct - 40)$;

Hct is the hematocrit, obtained from analysis of the individual's blood;

*K(shape*sex*age)* is a coefficient of the individual's body, being:

527.3 –(3.1 * (Actual Age –20)), for men younger than 20 years old;

527.3, for men from 20 to 40 years old;

527.3 + (3.1 * (Actual Age –40)), for men older than 40 years old;

587.6 –(2.9 * (Actual Age –18)), for women younger than 18 years old;

587.6, for women from 18 to 50 years old;

587.6 + (2.9 * (Actual Age –50)), for women older than 50 years old;

δr is the amplitude value of the change of the individual's basic body resistance R at the anacrotic (systolic) portion of a cardiac cycle;

R is the individual average basic body resistance during one cardiac cycle;

$H_{corr.}$ is a corrected height of the individual, given by:

$$H_{corr} = (H_{real} + 2) \quad \text{if} \quad \frac{\text{legs length}}{\text{body length}} = 0.66 \pm 0.04$$

or

$$H_{corr} = (H_{real} - 2) \quad \text{if} \quad \frac{\text{legs length}}{\text{body length}} = 0.54 \pm 0.04$$

or

$$H_{corr} = (H_{real}) \quad \text{if} \quad 0.62 \geq \frac{\text{legs length}}{\text{body length}} \geq 0.58$$

$\alpha + \beta$ is duration of a cardiac cycle, being a sum of its anacrotic and catacrotic portion;

β is duration of the catacrotic portion of a cardiac cycle;

Kel is a coefficient depending on ion concentration in the individual's blood plasma, calculated based on the blood analysis and being given by:

a) for an individual exposed to a hemodialysis

Kel = sum of the blood concentrations at $\frac{Na^{+}+K^{+}+Mg^{+}+Ca^{+}}{142+13}$

b) for other individuals

Kel = blood concentration of $\frac{Na^{+}}{142}$;

K_w is a weight coefficient, being a ratio $\frac{Actual\ weight}{Ideal\ weight}$, where Ideal weight being obtained from International Tables of ideal weights;

IB is an Index Balance, reflecting ratio between the measured volume of extracellular fluids and the individual's proper volume of extracellular fluids.

22. A method according to Claim 20, wherein the Index Balance is calculated based on the following formula:

$$\frac{R_{ind.prop}}{R_{measured}}$$

where *R measured* is the measured resistive component of the individual's bioimpedance, not including the individual's skin resistance;

$R_{ind.\ prop.}$ is a proper value of the resistive component of the indivudual's bioimpedance being calculated according to the two following formulae:

$$\frac{0.42H^2}{0.47W - 8.30} \quad \text{for men}$$

$$\frac{0.42\ H^2}{0.37\ W - 4.96} \quad \text{for women}$$

where H is the individual's height, and

W is the individual's actual weight.

23. The method according to any one of claims 15, 17, 18, 19, wherein said attaching step comprises:

attaching first basic pair of electrodes to the individual, by attaching one electrode of said pair on one arm or leg and another electrode of said pair on another arm or leg;

attaching a pair of auxiliary electrodes by attaching each auxiliary electrode to one of the arms or legs to which the basic pair of electrodes are attached and positioning the auxiliary electrodes on a more distal portion of the arms or legs than the basic pair;

said measuring step comprises:

measuring impedance comprising a first step in which current is passed and potential is measured using the basic pair of electrodes, and a second step wherein current is passed through the auxiliary electrodes and potential measured through the basic electrodes, in a tetrapolar measurement mode;

calculating the difference between the potential measured in the first step and the potential measured in the second step to calculate resistance of the skin of the individual from said difference;

continuously reducing the resistance of the skin of the individual from a value of said active component of the bioimpedance of the individual.

24. A non-invasive medical system for accurately determining at least one cardiorespiratory parameter of the human body and/or diagnosing of cardiorespiratory and blood circulation diseases, said device comprising:

at least two electrodes,

an electrical bioimpedance measuring unit for measuring bioimpedance of a human body, coupled to the electrodes and including a high stability amplitude alternating current source and an electronic circuit for automatic derivation of an active component of said bioimpedance; and

a computer coupled to the electrical bioimpedance measuring unit for calculating an average value of measured parameter parameter of the individual, the average value being of a number of values of said parameter for a number of cardiac cycles during a respiratory cycle, each parameter being calculated from said active component using a semi-empiric formula applicable to integral bioimpedance measurements, the computer being further coupled to a display for displaying said average value.

25. The system according to claim 24, comprising a plurality of electrodes for multi channel bioimpedance measurement, said electrodes including four basic electrodes applied to the distal parts of arms and legs, respectively, of the individual;

a pair of auxiliary electrodes for measuring a skin resistance of the individual and being applied to two of arms and legs of the individual and positioned more distal than corresponding basic electrodes;

four additional electrodes located one on each of a hip and a shoulder of the individual, and;

automatic multiplexing means for performing said multi–channel bioimpedance measurements.

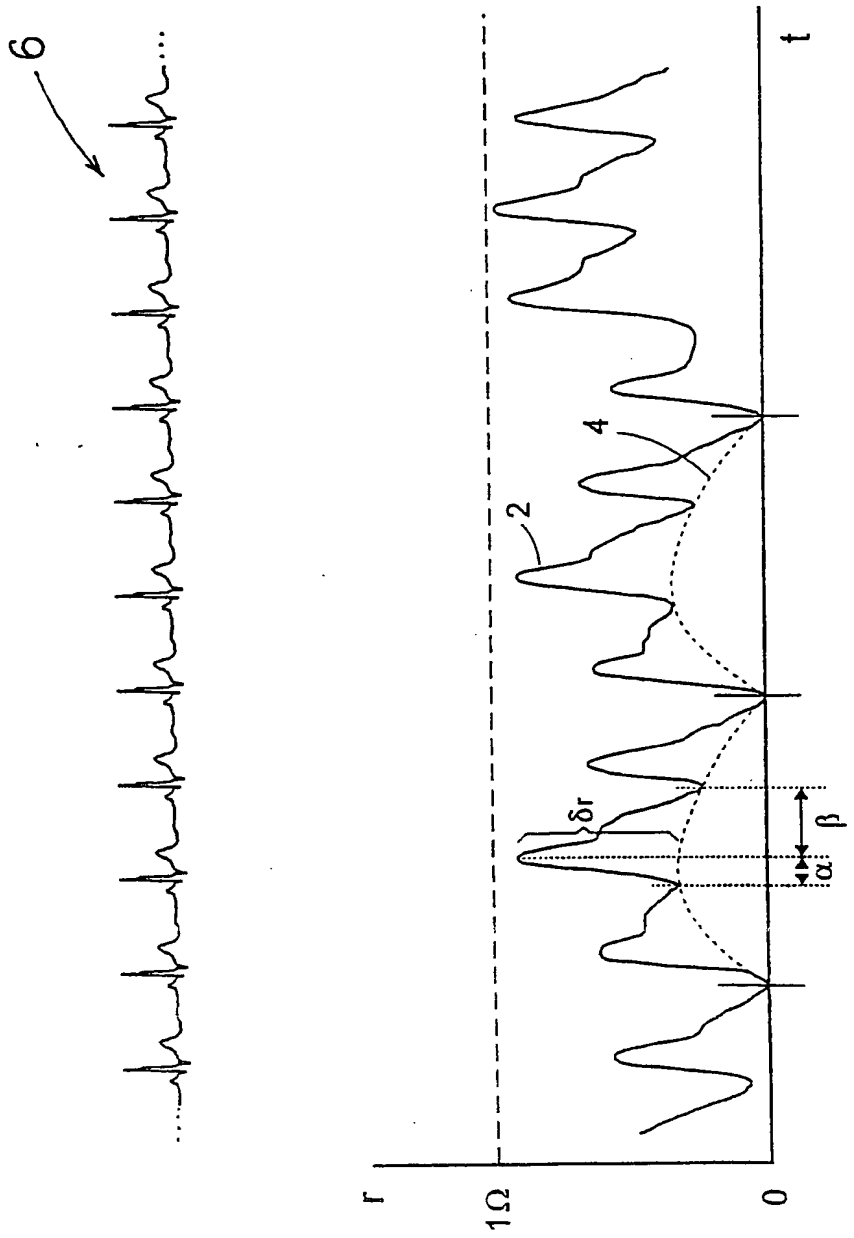


Fig. 1

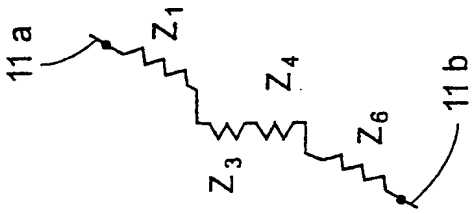

11 a
Z1
Z4
Z6
Z3
11 b

Fig. 2B

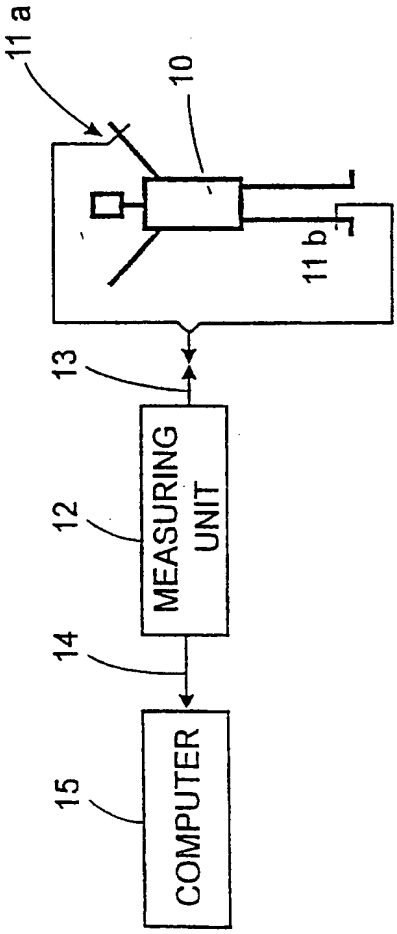

11 a
10
11 b
13
12
MEASURING UNIT
14
15
COMPUTER

Fig. 2A

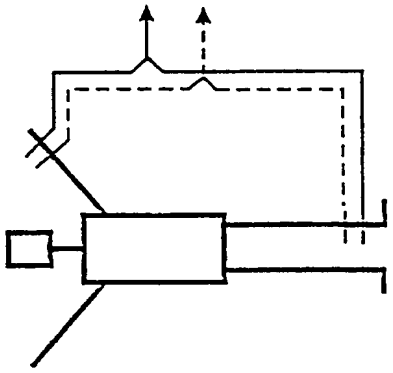


Fig.2E

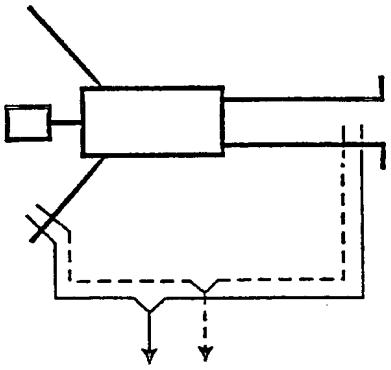


Fig.2D

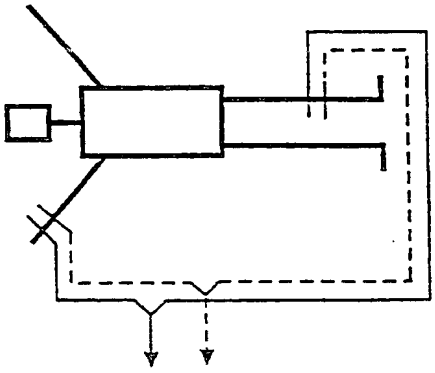


Fig.2C

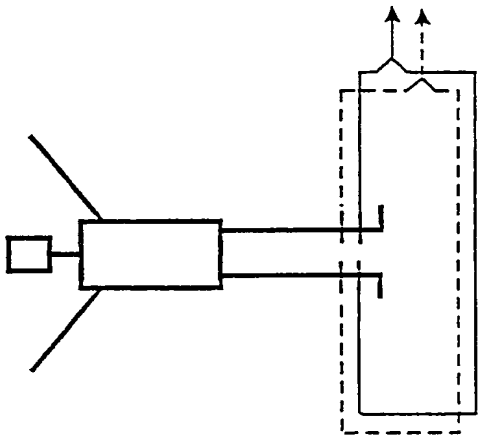


Fig.2G

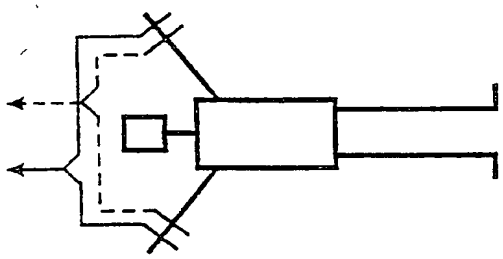


Fig.2F

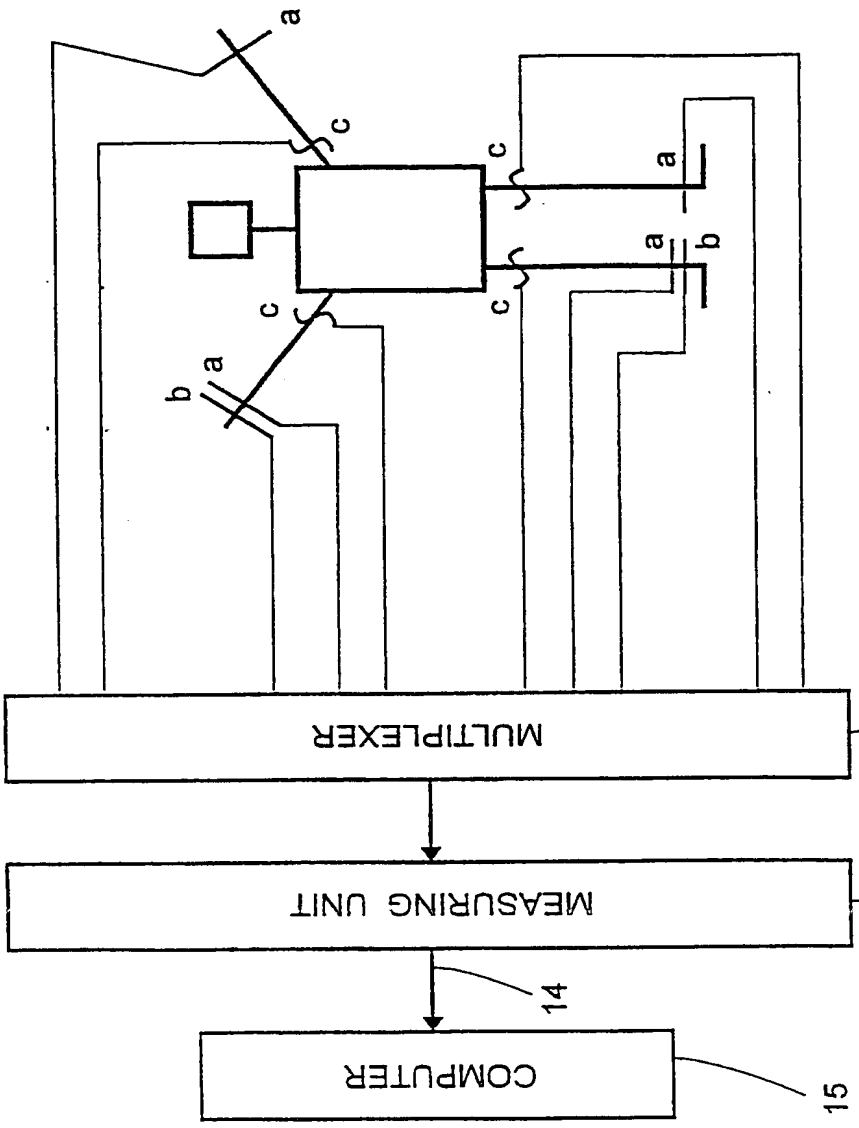

a
c
c
a
a
b
c
c
b
a
MULTIPLEXER
16
MEASURING UNIT
12
14
COMPUTER
15

Fig.2H

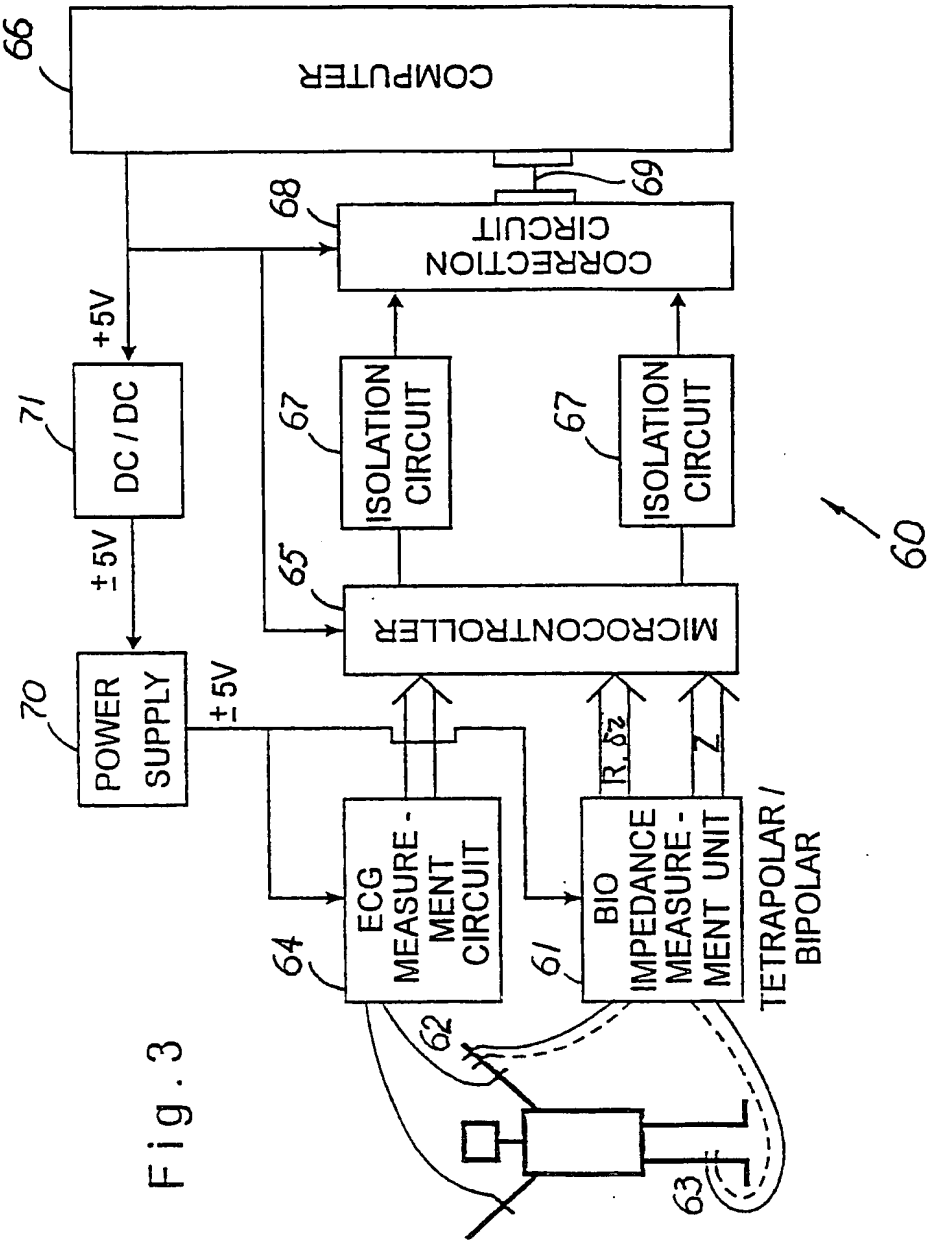

66
COMPUTER
69
68
CORRECTION CIRCUIT
+5V
71
DC / DC
67
ISOLATION CIRCUIT
67
ISOLATION CIRCUIT
60
± 5V
65
MICROCONTROLLER
70
POWER SUPPLY
± 5V
R, δz
Z
ECG MEASURE-MENT CIRCUIT
BIO IMPEDANCE MEASURE-MENT UNIT
TETRAPOLAR / BIPOLAR
64
61
62
63

Fig. 3

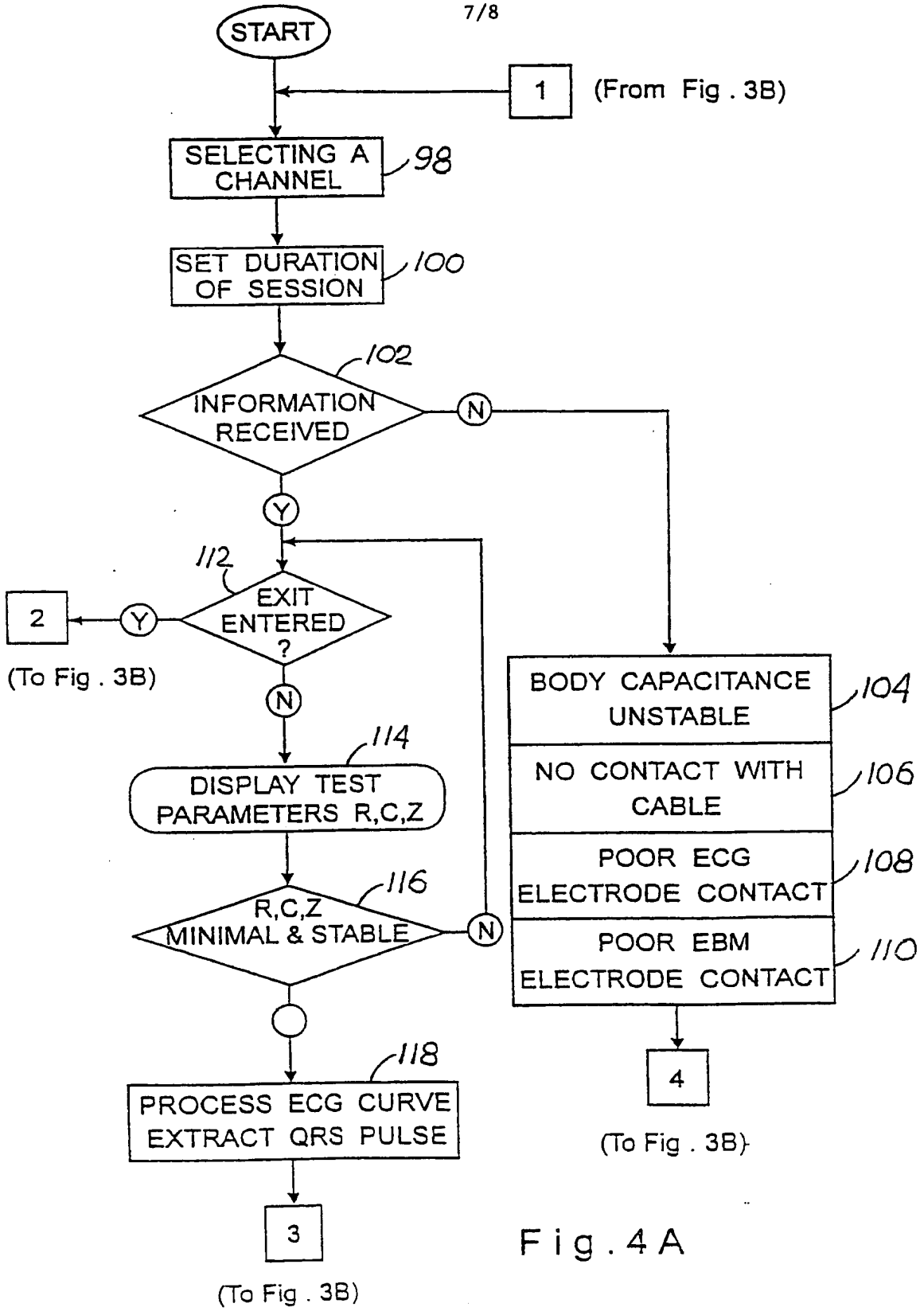

START
1
(From Fig . 3B)
SELECTING A CHANNEL
98
SET DURATION OF SESSION
100
102
INFORMATION RECEIVED
N
Y
112
EXIT ENTERED ?
Y
2
(To Fig . 3B)
N
114
DISPLAY TEST PARAMETERS R,C,Z
116
R,C,Z MINIMAL & STABLE
N
118
PROCESS ECG CURVE EXTRACT QRS PULSE
3
(To Fig . 3B)
BODY CAPACITANCE UNSTABLE
104
NO CONTACT WITH CABLE
106
POOR ECG ELECTRODE CONTACT
108
POOR EBM ELECTRODE CONTACT
110
4
(To Fig . 3B)

Fig . 4A

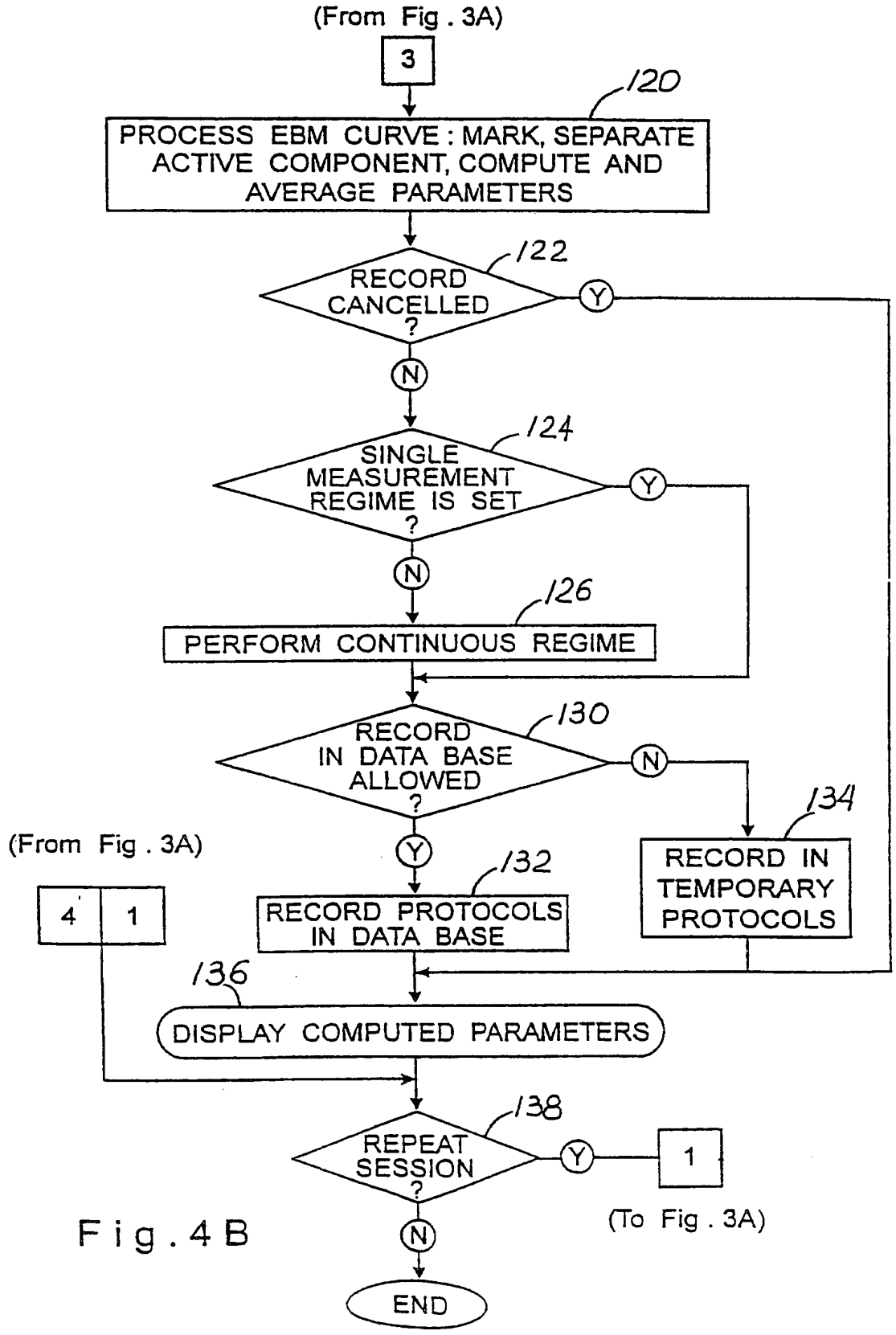

(From Fig . 3A)
3
120
PROCESS EBM CURVE : MARK, SEPARATE ACTIVE COMPONENT, COMPUTE AND AVERAGE PARAMETERS
122
RECORD CANCELLED ?
Y
N
124
SINGLE MEASUREMENT REGIME IS SET ?
Y
N
126
PERFORM CONTINUOUS REGIME
130
RECORD IN DATA BASE ALLOWED ?
N
Y
134
RECORD IN TEMPORARY PROTOCOLS
(From Fig . 3A)
4
1
132
RECORD PROTOCOLS IN DATA BASE
136
DISPLAY COMPUTED PARAMETERS
138
REPEAT SESSION ?
Y
1
(To Fig . 3A)
N
END

Fig . 4 B

INTERNATIONAL SEARCH REPORT

Intern.. .onal Application No
PCT/IL 97/00174

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61B5/05 A61B5/0205

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 469 859 A (N.I.MDICAL LTD) 28 November 1995 cited in the application see the whole document	1-25
A	WO 93 10706 A (SOMNUS CORPORATION) 10 June 1993 see page 9, line 8 - page 11, line 22	1,11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
18 February 1998	26/02/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lemercier, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ...nal Application No
PCT/IL 97/00174

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5469859 A	28-11-95	IL 102300 A	23-07-96
		EP 0575984 A	29-12-93
		JP 7031604 A	03-02-95
WO 9310706 A	10-06-93	US 5353793 A	11-10-94
		AU 2908792 A	28-06-93
		EP 0615424 A	21-09-94
		US 5564429 A	15-10-96
		US 5348008 A	20-09-94